

ONLINE FIRST

Evidence for Ordering of Alzheimer Disease Biomarkers

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Objective: To empirically assess the concept that Alzheimer disease (AD) biomarkers significantly depart from normality in a temporally ordered manner.

Design: Validation sample.

Setting: Multisite, referral centers.

Participants: A total of 401 elderly participants in the Alzheimer's Disease Neuroimaging Initiative who were cognitively normal, who had mild cognitive impairment, or who had AD dementia. We compared the proportions of 3 AD biomarker values (the A β 42 level in cerebrospinal fluid [CSF], the total tau level in CSF, and the hippocampal volume adjusted for intracranial volume [hereafter referred to as the adjusted hippocampal volume]) that were abnormal as cognitive impairment worsened. Cut points demarcating normal vs abnormal for each biomarker were established by maximizing diagnostic accuracy in independent autopsy samples.

Main Outcome Measures: Three AD biomarkers (ie, the CSF A β 42 level, the CSF total tau level, and the adjusted hippocampal volume).

Results: Within each clinical group of the entire sample (n=401), the CSF A β 42 level was abnormal more often than was the CSF total tau level or the adjusted hippocampal volume. Among the 298 participants with both

baseline and 12-month data, the proportion of participants with an abnormal A β 42 level did not change from baseline to 12 months in any group. The proportion of participants with an abnormal total tau level increased from baseline to 12 months in cognitively normal participants ($P=.05$) but not in participants with mild cognitive impairment or AD dementia. For 209 participants with an abnormal CSF A β 42 level at baseline, the percentage with an abnormal adjusted hippocampal volume but normal CSF total tau level increased from baseline to 12 months in participants with mild cognitive impairment. No change in the percentage of MCI participants with an abnormal total tau level was seen between baseline and 12 months.

Conclusions: A reduction in the CSF A β 42 level denotes a pathophysiological process that significantly departs from normality (ie, becomes dynamic) early, whereas the CSF total tau level and the adjusted hippocampal volume are biomarkers of downstream pathophysiological processes. The CSF total tau level becomes dynamic before the adjusted hippocampal volume, but the hippocampal volume is more dynamic in the clinically symptomatic mild cognitive impairment and AD dementia phases of the disease than is the CSF total tau level.

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B IOMARKERS OF ALZHEIMER disease (AD) occupy an essential place in recently formulated diagnostic criteria for AD,¹⁻⁵ in which their role is to identify the pathophysiological processes underlying cognitive impairment or to help predict time to dementia.⁶⁻¹⁵ These biomarkers are also increasingly used in clinical trials as both inclusion criteria and outcome measures.

At present, 5 AD biomarkers are sufficiently validated to be used in therapeutic trials, in large observational research

studies, and, on occasion, for clinical diagnostic purposes.¹⁶⁻¹⁹ The major biomarkers of brain A β deposition are a low level of A β 42 in cerebrospinal fluid (CSF) and a positive finding using positron emission tomographic amyloid imaging.²⁰⁻³⁰ Biomarkers of neuronal injury or neurodegeneration are elevated levels of total tau (t-tau) and phosphorylated tau in CSF,³¹⁻³³ decreased fludeoxyglucose F 18 uptake in the temporoparietal cortex determined using positron emission tomography,³⁴⁻³⁶ and atrophy in medial, basal, and lateral temporal lobes and in the medial parietal

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isocortex determined by using structural magnetic resonance imaging (MRI).³⁷⁻⁴³

Some of us recently proposed a hypothetical model of AD pathophysiology^{44,45} describing the temporal evolution of these 5 biomarkers based on the assumption that they do not change suddenly or simultaneously but rather over many years in an ordered, more sequential manner and that, likewise, they approach a pathological level in an ordered manner. The model does not assume a start-stop sequence whereby 1 biomarker changes then stops, the next changes then stops, etc. Rather, the model assumes that the maximum rate of change moves from 1 class of biomarker to the next, and, as the disease progresses, all biomarkers become progressively more abnormal simultaneously, albeit at rates that change over time in an ordered manner. It was proposed as a hypothetical biomarker cascade with validation awaiting additional data.

Empirical testing of this hypothetical biomarker cascade model^{44,45} can be approached in various ways⁴⁶; however, all testing methods require that different biomarkers be directly compared with each other in the same individuals. This can be conceptualized as plotting all biomarker values on a common graph with the vertical axis representing biomarker severity and the horizontal axis representing disease stage and/or time. Our present objective was to evaluate some aspects of the hypothetical biomarker cascade model by characterizing the prevalence of biomarker abnormalities at different disease stages defined by clinical cohort and by results of a Mini-Mental State Examination (MMSE). Comparing the proportions of participants with abnormal biomarker values allowed us to express significant biomarker deviations from normal in the same units for each biomarker. Cut points denoting abnormality for each biomarker were derived from independent autopsy cohorts, which limited our analysis to 3 of the 5 major AD biomarkers: the A β 42 level in CSF, the t-tau level in CSF, and the hippocampal volume adjusted for intracranial volume (hereafter referred to as the adjusted hippocampal volume that was determined using structural MRI). Our objective was to test the hypothesis that the CSF A β 42 level, CSF t-tau level, and adjusted hippocampal volume significantly depart from normality in a temporally ordered manner as disease progresses.

METHODS

PARTICIPANTS

All Alzheimer's Disease Neuroimaging Initiative (ADNI) participants who had usable baseline data on CSF A β 42 level, CSF t-tau level, and adjusted hippocampal volume were considered for our analysis. We also analyzed serial (baseline and 12-month) data if both CSF and structural MRI data were obtained at the 12-month visit. Written informed consent was obtained for participation in these studies, as approved by the institutional review board at each of the participating centers.

CSF METHODS

A standardized protocol was implemented in ADNI to quantify biomarker concentrations in each of the CSF baseline ali-

quots using a multiplex xMAP Luminex platform (Luminex Corp, Austin, Texas) with INNO-BIA AlzBio3 (Innogenetics, Ghent, Belgium) immunoassay kit–based reagents that was validated in Vanderstichele et al⁴⁷ and Shaw et al.³² Details can be found at <http://www.adni-info.org>.

MRI METHODS

All participants were scanned at 1.5 T with a 3-dimensional magnetization-prepared rapid-acquisition gradient-echo imaging sequence.⁴⁸ All images were corrected for image distortion due to gradient nonlinearity using GradWarp,⁴⁹ for B1 nonuniformity as necessary,⁴⁸ and for residual inhomogeneity using N3⁵⁰ with a software pipeline running at the Mayo Clinic Rochester in Minnesota. Hippocampal and intracranial volumes for both the autopsy sample and the main ADNI analysis sample were measured at Mayo Clinic using FreeSurfer software version 4.5.0.⁵¹ Each participant's raw hippocampal volume was adjusted by his or her total intracranial volume (adjusted hippocampal volume).⁵²

METHOD OF DEFINING CUT POINTS

To create a common analytic framework to compare different biomarkers, we elected to define each biomarker measure as either normal or abnormal. This requires that a cut point be established in the continuous distribution of values for each biomarker. Arguably the least biased and most valid approach to establishing biomarker cut points is to use an independent cohort in which ground truth is established by autopsy. Cut points for CSF A β 42 and t-tau levels were established by Shaw et al^{32,53} using an ADNI-independent autopsy cohort of participants who were observed at the University of Pennsylvania Alzheimer's Disease Core Center and who were diagnosed by use of National Institute on Aging (NIA)–Reagan criteria.²⁰ The cut points were chosen to maximize accuracy in separating high-probability from low-probability autopsy-proven AD.

To our knowledge, however, cut points have not been established for hippocampal atrophy using an independent autopsy data set that employed imaging methods identical to those used in the ADNI. To obtain an adjusted hippocampal volume cut point, we used an independent sample of 53 participants at the Mayo Clinic who had an MRI performed within 3.5 years before death and an autopsy diagnosis of high or low probability of AD using NIA-Reagan criteria. These participants had been enrolled in the Mayo Alzheimer's Disease Patient Registry or the Mayo Alzheimer's Disease Research Center. Our cut point was based on first calculating an adjusted hippocampal volume using the formula $AHV = HV - (2.546201 + 0.002139314 \times \text{intracranial volume})$, where AHV (as the adjusted hippocampal volume) is the residual value obtained after regressing HV (as the hippocampal volume) vs intracranial volume. Next, we performed a receiver operating characteristic curve analysis and chose a cut point in order to maximize accuracy in separating high-probability from low-probability autopsy-proven AD. That is, we chose the cut point to maximize sensitivity–(1–specificity).

STATISTICAL METHODS

Each participant had 3 binary outcomes for his or her baseline visit defined as normal ($y=0$) or abnormal ($y=1$) for each of the 3 biomarkers. Because these can be considered repeated-measures data having a binary outcome, we used generalized estimating equations with the logit link and an exchangeable working correlation matrix to estimate and compare the proportion of participants having an abnormal biomarker. Our predictors were clinical group (cognitively normal [CN] partici-

pants vs participants with mild cognitive impairment [MCI] vs participants with AD dementia), biomarker, and their interaction. We used likelihood ratio tests to perform a global test of biomarker differences, after including the clinical group in the model, and to test for an interaction between clinical group and biomarker. We used Wald tests to perform pairwise comparisons of abnormality of a biomarker separately within each clinical group. This analysis was then repeated, replacing clinical group with the MMSE, modeled as a restricted cubic spline with knots at the 10th, 50th, and 90th percentiles of the MMSE distribution. We also performed a subset analysis among those with an abnormal baseline CSF A β 42 level and examined the CSF t-tau levels and adjusted hippocampal volumes within groups.

Among those participants who also had a 12-month visit, we used baseline and 12-month data and fit a generalized estimating equations model that included group, visit, and biomarker along with all interactions. From this model, we estimated separate rates of biomarker abnormality by group, time point, and biomarker. We also performed a subset analysis among those participants with abnormal baseline CSF A β 42 levels and examined within-group change in CSF t-tau levels and adjusted hippocampal volumes from baseline to 12 months.

RESULTS

BIOMARKER CUT-POINT VALUES

The cut point for defining abnormal hippocampal volume was based on a sample of 43 participants from Mayo Clinic who had a structural MRI performed before they died and an autopsy diagnosis of high-probability AD (24 [56%] of whom were women, with a median age at death of 85 years) and 10 participants from Mayo Clinic who had a structural MRI performed before they died and an autopsy diagnosis of low probability AD (6 [60%] of whom were women, with a median age at death of 85 years). This Mayo Clinic autopsy cohort was older than the ADNI cohort (median [interquartile range {IQR}], 83 [76-88] years vs 75 [71-80] years; $P < .001$), had a higher percentage of women (57% vs 40%; $P = .03$), and had more severe cognitive impairment as measured using the MMSE (median [IQR], 20 [13-26] points vs 27 [25-29] points; $P < .001$) (eTable 1; <http://www.archneuro.com>). The optimal adjusted hippocampal volume ratio cut-point value in the autopsy cohort was 0.48 (eFigure 1). With this cut point, participants with low-probability AD (based on NIA-Reagan criteria) in the MRI training sample were separated from participants with high-probability AD with a classification accuracy of 79%, a sensitivity of 74%, and a specificity of 100%. Overall discrimination was high with an area under the receiver operating characteristic curve of 0.90. Previously established cut-point values for the CSF A β 42 level and the CSF t-tau level were 192 and 92 pg/mL, respectively, and they were used to define abnormal studies.³²

MAIN ANALYSIS

The main analysis included 401 participants in the ADNI (ie, 116 CN participants, 196 participants with MCI, and 89 participants with AD dementia) with baseline data. In total, 298 participants had baseline and 12-month data.

The baseline age distributions varied somewhat among the 3 groups of participants (analysis of variance; $P = .03$), and there were differences in the percentage of women that ranged from 33% of women with MCI to 49% of CN women (**Table 1**). The MMSE score and the percentage of APOE ϵ 4 carriers varied by clinical group in the expected manner.

For each of the 3 biomarkers evaluated, the median baseline group values became more abnormal ($P < .001$, linear trend test) (Table 1, **Figure 1**), and the percentage of participants with abnormal biomarker findings (Table 1, **Figure 2A**) increased in an ordered manner in the CN, MCI, and AD groups. The same pattern held at 12 months. The percentage of participants with abnormal biomarker findings increased monotonically for each biomarker with decreasing MMSE score (Figure 2B). A supplement to Figure 2 (eFigure 2) shows plots of individual patient trajectories for each biomarker within the clinical diagnosis groups.

Among all 401 participants at baseline, the CSF A β 42 level was abnormal more often than was the CSF t-tau level or the adjusted hippocampal volume in each clinical group ($P < .001$ across all pairwise tests) (**Table 2**). The percentage of participants with an abnormal CSF t-tau level was greater than the percentage of participants with an abnormal adjusted hippocampal volume among CN participants (21% vs 8%; $P = .003$) but did not differ among participants with MCI or AD dementia (Table 2).

We performed a subanalysis of baseline CSF t-tau levels and adjusted hippocampal volumes among only those participants (47 CN participants, 145 participants with MCI, and 82 participants with AD) who had an abnormal CSF A β 42 level at baseline. These participants were similar to the participants who had a CSF A β 42 level in the normal range by age (median [IQR], 76 [72-80] years vs 75 [71-80] years; $P = .78$) and sex (39% vs 40% of participants were women; $P = .97$), but they had more severe cognitive impairment as measured using the MMSE (median [IQR], 26 [25-29] points vs 29 [27-29] points; $P < .001$) (eTable 2). The percentage of these participants who had an abnormal CSF A β 42 level along with an abnormal CSF t-tau level and an abnormal adjusted hippocampal volume increased monotonically by clinical group in the following order: CN participants, participants with MCI, and participants with AD dementia (Figure 2C), and increased monotonically with decreasing MMSE score (Figure 2D). In this subanalysis, the CSF t-tau level was abnormal more often than was the adjusted hippocampal volume in CN participants. There was a trend of more abnormal CSF t-tau levels than abnormal hippocampal volumes in participants with MCI but no difference in participants with AD dementia (Table 2).

Among the 298 participants with both baseline and 12-month data, the proportion of participants with an abnormal CSF A β 42 level did not change from baseline to 12 months in any diagnosis group ($P = .15$ for the CN group, $P = .15$ for the MCI group, and $P = .33$ for the AD group) (**Figure 3A**). The proportion of participants with an abnormal CSF t-tau level increased from baseline to 12 months in CN participants ($P = .05$) but not in participants with MCI ($P = .40$) or AD dementia ($P > .99$),

Table 1. Characteristics of 401 Elderly Participants in the Alzheimer's Disease Neuroimaging Initiative at Baseline and 12 Months by Baseline Diagnosis

Characteristic	Baseline Diagnosis					
	Cognitively Normal		Mild Cognitive Impairment		Alzheimer Disease	
	Baseline (n = 116)	12 mo (n = 93)	Baseline (n = 196)	12 mo (n = 146)	Baseline (n = 89)	12 mo (n = 59)
Female participants, No. (%)	57 (49)	45 (48)	65 (33)	46 (32)	37 (42)	25 (42)
APOE ε4 carriers, No. (%)	27 (23)	22 (24)	107 (55)	80 (55)	64 (72)	46 (78)
Age, y						
Median (IQR)	76 (72-78)	76 (73-79)	75 (70-80)	76 (72-81)	77 (72-81)	79 (74-82)
Range	62-90	63-91	55-89	59-90	65-89	67-89
MMSE score						
Median (IQR)	29 (29-30)	29 (28-30)	27 (25-28)	27 (24-28)	24 (22-25)	23 (19-25)
Range	25-30	25-30	23-30	17-30	20-27	5-27
CSF Aβ42 level, pg/mL						
Median (IQR)	221 (157-248)	222 (160-244)	146 (129-201)	143 (124-168)	140 (119-153)	135 (125-148)
Range	79-298	84-299	48-299	80-296	75-289	75-271
Participants with Aβ42 level <192 pg/mL, No. (%)	47 (41)	38 (41)	145 (74)	114 (78)	82 (92)	58 (98)
CSF t-tau level, pg/mL						
Median (IQR)	63 (48-85)	67 (51-95)	87 (64-128)	96 (66-139)	115 (80-144)	115 (90-146)
Range	29-200	27-175	28-463	32-363	32-349	35-273
Participants with t-tau level >93 pg/mL, No. (%)	24 (21)	25 (27)	88 (45)	75 (51)	59 (66)	42 (71)
AHV						
Median (IQR)	1.65 (1.16-2.19)	1.53 (1.06-2.16)	0.58 (0.03-1.33)	0.17 (-0.41 to 1.06)	-0.22 (-0.75 to 0.50)	-0.65 (-1.04 to 0.08)
Range	-0.34 to 3.50	-0.20 to 3.94	-1.81 to 3.81	-2.12 to 4.00	-2.00 to 1.94	-2.33 to 1.64
Participants with HV <0.48, No. (%)	9 (8)	8 (9)	87 (44)	88 (60)	66 (74)	49 (83)

Abbreviations: AHV, hippocampal volume adjusted for intracranial volume; CSF, cerebrospinal fluid; IQR, interquartile range; MMSE, Mini-Mental State Examination; t-tau, total tau.

although the absolute levels of t-tau in the CN group were far lower than in the MCI group. There was no difference in the proportion of participants with an abnormal adjusted hippocampal volume between the CN group ($P > .99$) and the AD group ($P = .16$), from baseline to 12 months, but there was a significant increase in the proportion of participants with an abnormal hippocampal volume in the MCI group.

The preceding paragraph describes the proportion of participants by group with abnormal biomarker values at baseline and 12 months. The change in biomarker values in native measurement units is seen in Figure 1. On average, the CSF Aβ42 levels did not change from baseline to 12 months in any group ($P = .52$, $P = .13$, $P = .51$ for the CN, MCI, and AD groups, respectively). On average, the CSF t-tau levels increased in the CN group ($P = .002$) but not in the MCI group ($P = .12$) or the AD group ($P = .36$). On average, the adjusted hippocampal volumes decreased in all groups ($P < .001$).

We also performed a subanalysis among only those participants ($n = 209$) who had an abnormal CSF Aβ42 level at baseline and who also had both baseline and 12-month data (Figure 3B). Neither the proportion of participants with an abnormal CSF Aβ42 level nor the proportion of participants with an abnormal CSF t-tau level changed from baseline to 12 months in any diagnosis

group. The proportion of participants with an abnormal adjusted hippocampal volume increased from baseline to 12 months for the MCI group ($P < .001$) but did not differ for the CN group ($P = .32$) or the AD group ($P = .16$).

COMMENT

Our overall objective was to test for evidence of temporal ordering of the CSF Aβ42 level, the CSF t-tau level, and the adjusted hippocampal volume.^{54,55} We were limited to evaluating these 3 AD biomarkers for which independent autopsy cohorts were available to select normal or abnormal cut points in an unbiased manner. A biomarker value for an individual participant at a given point in time (and, by extension, the percentage of abnormal values across a group at a given disease stage) is a function of 2 phenomena: (1) the elapsed time from the initial deviation of the biomarker away from normality to the present and (2) the average rate of change of the biomarker over this period of time. An analogy to motion would be distance traveled from abnormality, average rate of change, and elapsed time. Our data consisted of measures of each biomarker value at a fixed point or points in time in participants who entered the study at different stages of the disease. We observed whether a

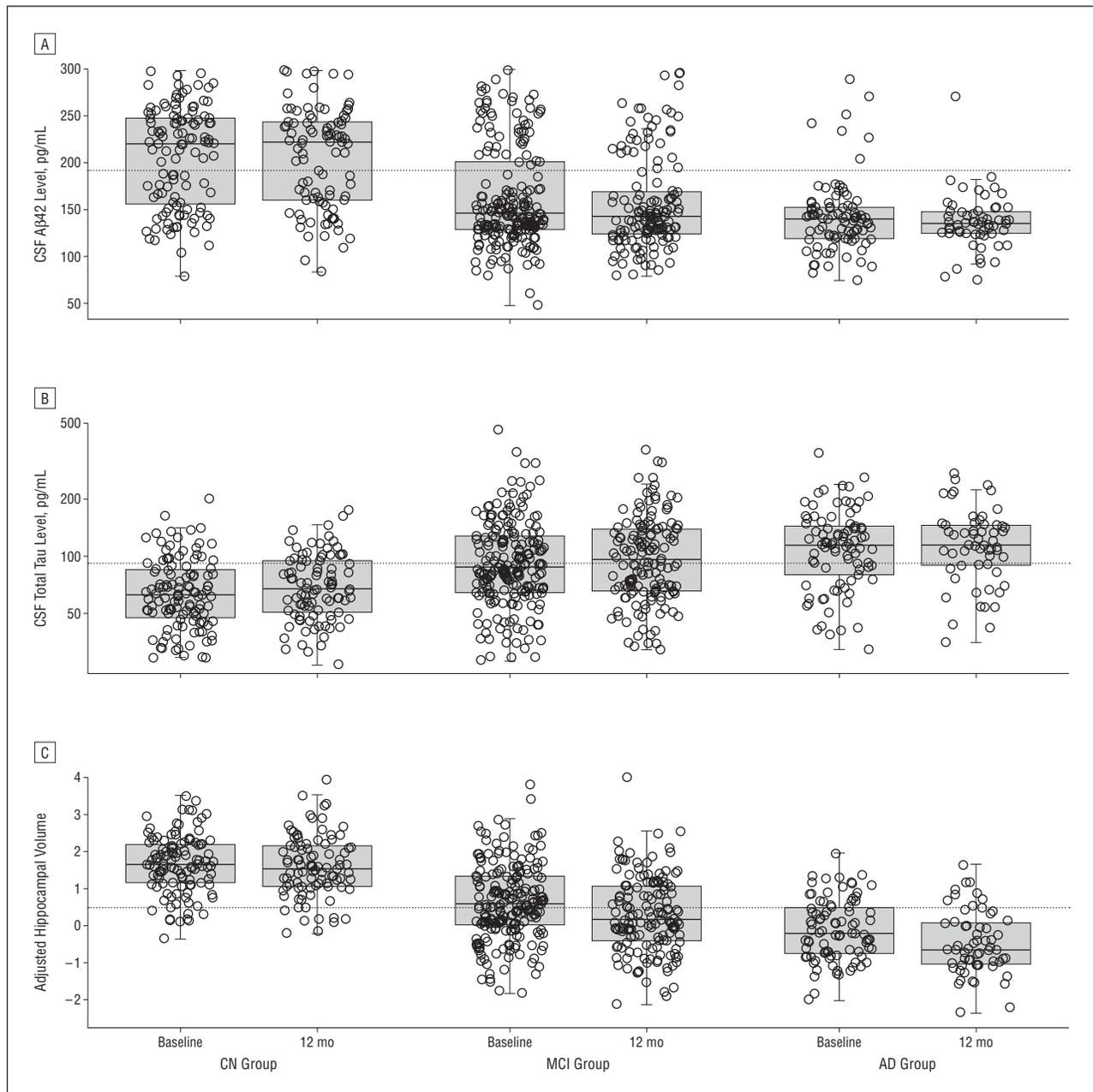


Figure 1. Box plots and superimposed data points showing the distribution of Alzheimer disease (AD) biomarkers by baseline diagnosis and visit. The horizontal line in each box indicates the median, whereas the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers above and below the box mark the largest and smallest data point that is within 1.5 times the interquartile range of the top and bottom of the box. A, For participants with both baseline and 12-month data, the cerebrospinal fluid (CSF) A β 42 level did not change from baseline to 12 months in the cognitively normal (CN) group ($P=.52$), the mild cognitive impairment (MCI) group ($P=.13$), or the AD group ($P=.51$). B, The CSF total tau level is shown on the log scale. It increased from baseline to 12 months in CN participants ($P=.002$) but not in participants with MCI ($P=.12$) or AD ($P=.36$). C, The adjusted hippocampal volume decreased from baseline to 12 months in all clinical groups ($P<.001$). The dotted horizontal line extending across all box plots represents the cut point denoting normal vs abnormal for each biomarker.

participant had reached a certain distance from normality but cannot individually identify the contributions from average rate of change and elapsed time. We can, however, draw valid inferences from our data about the combined effect of time elapsed from onset and average rate of change, and we refer to this as the relative dynamic ordering of biomarkers.

The data presented herein support several key principles in our recently proposed hypothetical biomarker cascade model.^{44,45} These include the following: (1) All

biomarkers become progressively more abnormal as participants' symptoms worsen clinically. (2) Reduction in the CSF A β 42 level denotes an upstream pathophysiological process that significantly departs from normality (ie, is dynamic) early in the pathophysiological cascade, while participants are clinically asymptomatic, but does not change greatly during the clinically symptomatic MCI and dementia phases of the disease. (3) The CSF t-tau level and the adjusted hippocampal volume are biomarkers of the downstream neurodegenerative patho-

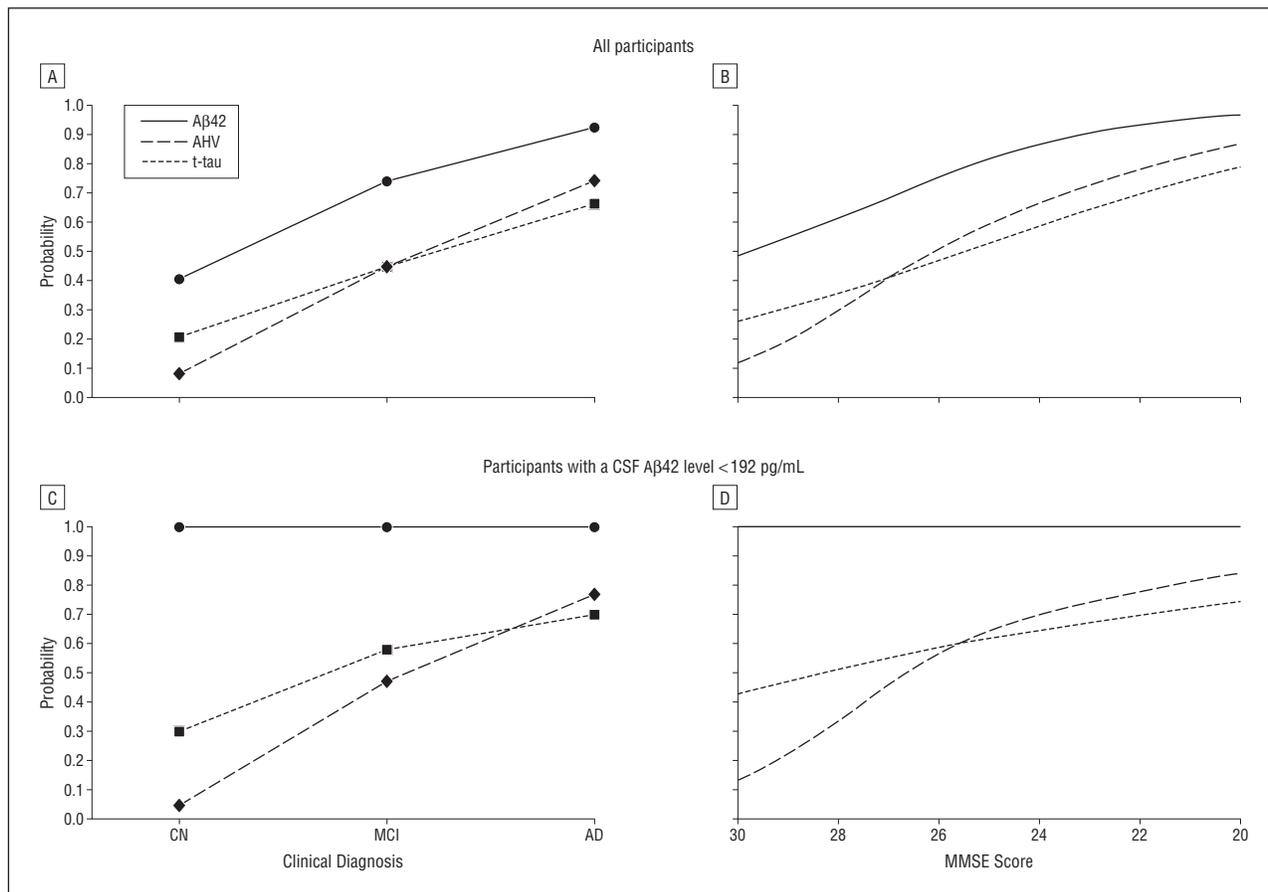


Figure 2. Estimated probability of abnormality for each Alzheimer disease (AD) biomarker in all participants (n=401) (A and B) and within the subset of participants with an abnormal cerebrospinal fluid (CSF) Aβ42 level at baseline (n=274) (C and D). Abnormality is shown by clinical diagnosis (ie, cognitively normal [CN], mild cognitive impairment [MCI], or AD) (A and C) and Mini-Mental State Examination (MMSE) score (B and D). The cutoffs used are 192 pg/mL for the CSF Aβ42 level, 93 pg/mL for the CSF total tau level (t-tau), and 0.48 for the adjusted hippocampal volume (AHV).

Table 2. Proportions of Abnormality Between Biomarkers by Clinical Group^a

Comparison	CN Group	P Value	MCI Group	P Value	AD Group	P Value
All participants (n = 401)						
Aβ42 vs total tau	41% vs 21%	<.001	74% vs 45%	<.001	92% vs 66%	<.001
Aβ42 vs AHV	41% vs 8%	<.001	74% vs 44%	<.001	92% vs 74%	<.001
Total tau vs AHV	21% vs 8%	.003	45% vs 44%	.92	66% vs 74%	.16
Participants with abnormal Aβ42 level (n = 274) ^b						
Total tau vs HV	30% vs 4%	.003	58% vs 47%	.07	70% vs 77%	.20

Abbreviations: AD, Alzheimer disease; AHV, hippocampal volume adjusted for intracranial volume; CN, cognitively normal; MCI, mild cognitive impairment.

^aBased on generalized estimating equations logistic model with an exchangeable correlation structure. The P values were determined from pairwise hypothesis tests comparing abnormality between 2 biomarkers for a given clinical group.

^bA level of less than 192 pg/mL of Aβ42 in cerebrospinal fluid, at baseline.

physiological process that are dynamic later as the participant approaches and moves through the clinically symptomatic phases of the disease.⁵⁶⁻⁶⁴ (4) Cognitive decline is more closely related to biomarkers of neuronal injury than to biomarkers of brain Aβ load.⁶⁵⁻⁷² (5) The CSF t-tau level is more dynamic earlier in the disease phase than is the adjusted hippocampal volume, but the proportions of the 2 biomarkers that are abnormal are similar in symptomatic participants such that the adjusted hippocampal volume “catches up” to the CSF t-tau level as symptoms worsen. This is supported visually by the

steeper slope of the adjusted hippocampal volume vs the CSF t-tau level in Figure 2.

The hypothetical model represents an idealized trajectory of an individual who progresses owing to pathologically pure AD dementia. Our sample, however, almost certainly consists of a mixture of participants, many of whom are on the AD pathway and many of whom are not (particularly those in the CN and MCI groups).⁷³⁻⁷⁸ The fact that both an elevated CSF t-tau level and hippocampal atrophy can occur in other conditions that lead to dementia,⁷⁹ such as cerebrovascular disease, has led to the belief that,

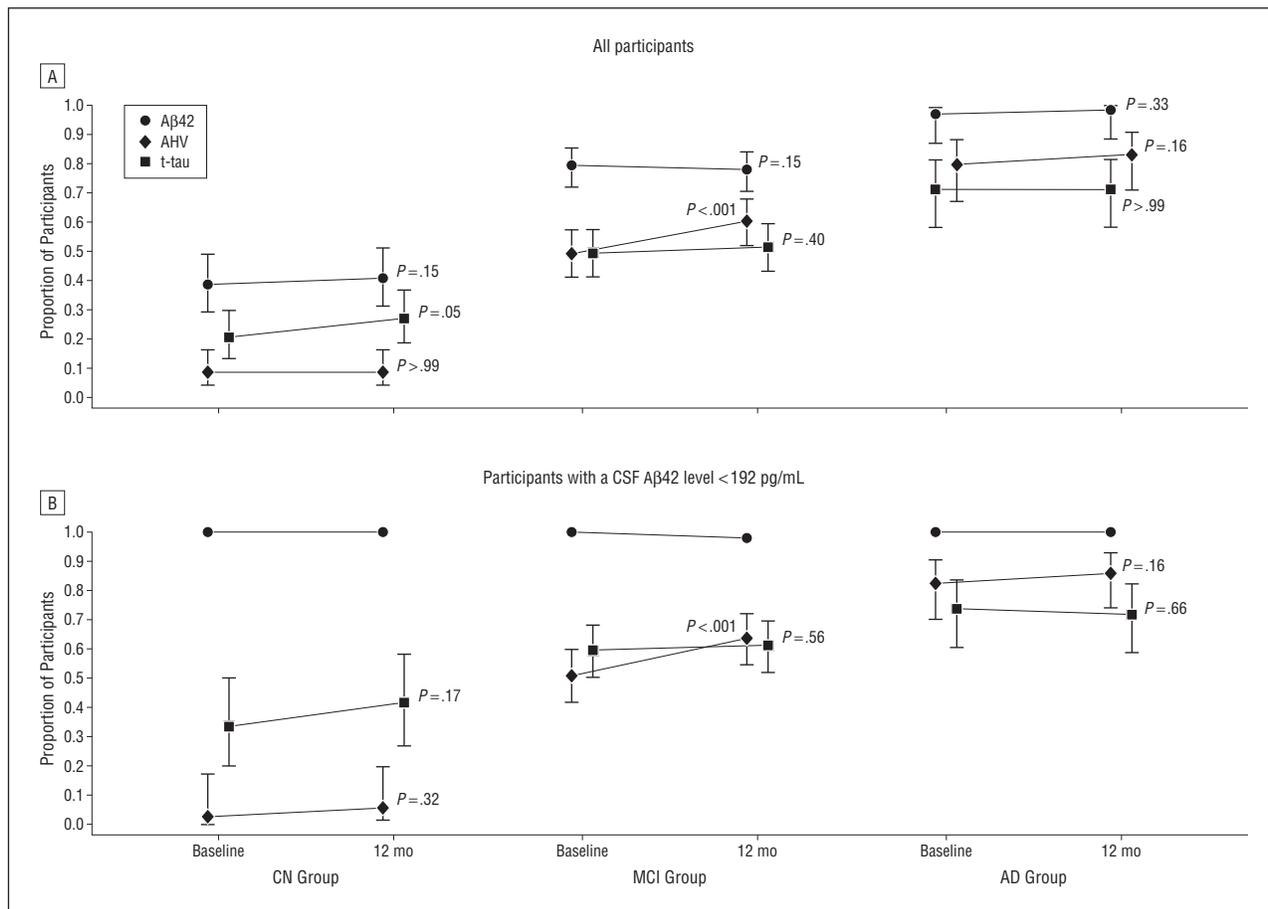


Figure 3. Estimated proportion of participants who had abnormal Alzheimer disease (AD) biomarker values at baseline and at 12 months shown by baseline clinical diagnosis for the subset of participants with serial data (n=298) (A) and for a subset of participants with serial data who had an abnormal cerebrospinal fluid (CSF) Aβ42 level at baseline (n=209) (B). Values are shifted slightly along the x-axis for the middle biomarker to reduce overlap in lines. The cutoffs used are 192 pg/mL for the CSF Aβ42 level, 93 pg/mL for the CSF total tau level (t-tau), and 0.48 for the adjusted hippocampal volume (AHV). CN indicates cognitively normal; MCI, mild cognitive impairment.

of the 3 biomarkers we examined, the CSF Aβ42 level should have the greatest specificity for AD.⁸⁰ Consequently, we performed a subanalysis of participants with an abnormal CSF Aβ42 level at baseline in order to isolate those participants who we were somewhat more confident were in the AD pathophysiological pathway.^{56,81-86} Our results concerning evidence for biomarker ordering led to similar conclusions in the “all-participants” sample and in the sample of participants with an abnormal CSF Aβ42 level.

Using the percent-abnormal metric might not seem to be an obvious first choice for comparing biomarkers. Other options, however, have proven to be untenable. For example, using biomarker values in native measurement units precludes direct comparisons of biomarkers because they are not on a common scale; z scores or percentiles are also not tenable because, by construction, half the participants in the sample must be above average for each biomarker, and half must be below average. This constraint would make it impossible to test our major question: is 1 biomarker abnormal more often than another at different stages of the disease? The obvious advantage of comparing biomarkers on a percent-abnormal basis is that the scoring method is standardized for all biomarkers over the entire cognitive continuum. A limitation is that the results are highly sensitive to the

cut-point values, and hence the validity of the analysis depends on selecting valid cut points for each biomarker. We used cut-point values for each biomarker that were based on an independent autopsy-verified sample, and we used the same pathological criteria for all biomarkers (ie, high or low probability of AD using the NIA-Reagan criteria). Although using cut points based on diagnostic sensitivity, rather than accuracy, in the autopsy reference standard might seem a better approach, we found that that is not the case. Imagine a biomarker with identical distributions in autopsy-proven high- vs low-probability AD. Fixing a cut point at a sensitivity of 90% in autopsy-proven high-probability AD would lead to the conclusion that 90% of cases of autopsy-proven low-probability AD had abnormal biomarker values and that the biomarker in question comes “early” in the pathophysiological cascade. This would clearly be erroneous. Thus, our choice of selecting cut points in a manner that is constrained by both sensitivity and specificity, as is done for all clinically applied diagnostic tests, seems prudent in our study.

Our hypothetical model^{44,45} was intended to represent an idealized trajectory that an individual follows from a time prior to the appearance of any AD pathophysiology in the brain through end-stage AD dementia, when

all biomarkers have become maximally abnormal. The optimal way to test this model would be to follow the trajectory of multiple biomarkers over several decades in a large group of participants who enter a study prior to the first appearance of any AD pathophysiology and are followed up through the symptomatic stages of the disease to autopsy. Given that the total course of the disease may span 30 years or more, it will take many years to accumulate the necessary data to construct a temporally accurate disease model. While the data are being accumulated, perhaps the only realistic approach to empirical analysis is to attempt to build models of disease in a piecewise fashion from individual participants who are at various stages in the disease course, as we have done here.

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